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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/779,389 | 02/07/01 | MCGALL G | 18547-040820 |

| EXAMINER |
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| PRASTHOFER, T |

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| ART UNIT | PAPER NUMBER |
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| 1627 | 5 |

**DATE MAILED:** 09/10/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary<br>file copy | Application No.<br>09/779,389 | Applicant(s)<br>MCGALL ET AL. | |
|---|---|---|---|
| | Examiner<br>Thomas W Prasthofer | Art Unit<br>1627 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

# Detailed Action

## Change of Examiner

The examiner of this application has changed from Barba Koroma to Thomas Prasthofer.

## Status of the Application

Receipt is acknowledged of a response to a restriction requirement on June 25, 2001 in Paper No.4.

## Status of the Claims

Claims 1-17 are pending in the present application. Claims 16 and 17 are withdrawn from further consideration as being drawn to non-elected inventions. Claims 1-15 are being examined on their merits.

## Information Disclosure Statement

The information disclosure statement (IDS) received May 11, 2001 is not presently with the case. Examiner has made attempts to locate the IDS without success. For this reason, examiner has not considered the references cited in the IDS. Examiner will continue to search for the IDS and will consider the references cited therein once the IDS has been located or a replacement IDS is received from applicant. Examiner regrets the inconvenience that this may cause applicant.

**Response to Restriction and Election of Species**

Applicant's election of Group I, claims 1-11 and 13-15 in Paper No. 4 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Groups I (claims 1-11 and 13-15) and II (claim 12) are rejoined by examiner. The restriction and election of species requirements are still considered proper and are made FINAL.

**Claims Rejections – 35 U.S.C. 112, second paragraph**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "non-oxidizing atmosphere" in claims 1-3, for example, is defined in the specification to mean " *an atmosphere or environment that produces less than 30% degradation of nucleic acid over a period of about 1 hour at ambient temperature (about 18 to about 25°C).*" The term "non-oxidizing atmosphere" requires a defined means of measuring degradation to be definite because the degradation of nucleic acids can be measured in different ways with different results. The term "degradation" is also open to interpretation because nucleic acid bases can be degraded with or without the breaking of phosphodiester linkages. Therefor, one measuring the degradation of nucleic acid would need to know what form of degradation is being measured and how it is to be measured for the term "*less than 30% degradation of nucleic acid*" to be definite.

B. It is not clear if the term "non-oxidizing atmosphere" in claims 1-3, for example, is intended to include an aqueous or organic solvent "environment" used during chemical synthesis. For the purpose of compact prosecution, examiner assumes that liquid (solvent0 environments are encompassed by the term.

C. In claim 4 it is not clear how a synthetic method can be conducted if "said atmosphere" is carbon-filtered air if the "environment" also includes solvents and reagents. If "said atmosphere" ("non-oxidizing atmosphere") is intended to exclude liquid environments, this should be made clear.

D. In claim 5 it is not clear how a synthetic method can be conducted if "said atmosphere" is an inert gas if the "environment" also includes solvents and reagents. If "said atmosphere" ("non-oxidizing atmosphere") is intended to exclude liquid environments, this should be made clear.

E. In claim 6 it is not clear how a synthetic method can be conducted if "said atmosphere" is argon if the "environment" also includes solvents and reagents. If "said atmosphere" ("non-oxidizing atmosphere") is intended to exclude liquid environments, this should be made clear.

F. In claims 7 and 9 it is not clear what the spatial orientation of the surface is relative to the light source. It is not clear of "a position opposite the surface comprising said immobilized nucleotides" intents the light to pass through the surface from the side of the surface opposite the immobilized nucleotides. For the purpose of compact prosecution, examiner interprets the term to mean that the light to passes through the surface from the side of the surface opposite the immobilized nucleotides.

G. In claim 11, the metes and bounds of "facility" are not clear. For example, if the method steps are performed under a hood, are the entire room and/or building required to maintain an ozone concentration of 0-5 ppb?

H. In claim 13 it is not clear if preformed nucleic acids are immobilized or if nucleic acids are synthesized on solid supports or both. Clarification is required.

**Claims Rejections – 35 U.S.C. 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. Claims 1, 2, 3, 8, 13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Terrett, N.K., "Combinatorial Chemistry" (1998) Oxford University Press, pp. 40-47 with Fodor et al. U.S. patent 5,424,186 (June 1995) cited to demonstrate the lack of degradation of oligonucleotides by ozone.

The Terrett reference discloses various methods of synthesizing oligonucleotide arrays on a solid supports. A "*non-oxidizing atmosphere*" is defined on page 6, lines 16-18 of the present specification as "*an atmosphere or environment that produces less than 30% degradation of nucleic acid over a period of about 1 hour at ambient temperature (about 18 to about 25°C).*" On page 45 (just above figure 3.13), for example, it is disclosed that an octanucleotide array was produced in four hours. The method involved the activation of a support, attaching nucleotides to the support in defined regions that are not "masked," the use of protecting groups, and cycles of nucleotide additions in which the pattern of the mask changes to allow reactions to occur at specified sites on the solid substrate (see page 43, second paragraph through page 45, first paragraph). The library was successfully used in hybridization studies, indicating that no substantial degradation had occurred. Had there been a degradation rate of 30% per hour during the synthesis, the majority of the first six base positions would have been degraded, based on an average of two bases synthesized per hour (8 positions/ 4 hours). Had this been the case, the hybridization assay would not have worked. One may conclude from the results of the hybridization assay that the library was synthesized in a "non-oxidizing atmosphere" and that the reference anticipates present claims 1, 2, and 13. Arrays of octanucleotides are disclosed on page 45, anticipating present claim 15.

With respect to present claim 3, the Terrett reference sites the VSLIPS technology of Fodor et al. on pages 40-45, which anticipates all of the method steps of present claim 3. The Terrett reference is silent as to the ozone concentration present during the synthesis of oligonucleotides by Fodor et al. at the top of page 45. To demonstrate that lower levels of ozone are inherent in the method of Fodor et al., examiner refers applicant to Fodor et al. U.S. patent 5,424,186 (June 1995) example 3, columns 66-68. The poly dT bound to a solid support was

able to hybridize to poly dA probes even after an overnight incubation in 1X SSPE buffer at 40 deg. C. Applicant's figure 1A indicates that concentrations of ozone as low as 5 ppb results in 70% degradation of poly T within 15 hours of exposure. It appears that the solutions used by Fodor et al. did not contain levels of ozone (e.g. 5 ppb) sufficient to cause degradation of poly dT oligomers and that present claim 3 is anticipated by Terrett's disclosure of Fodor et al.

The source of UV light used in light-directed parallel synthesis as disclosed on page 41 of Terrett is on the same side of the glass slide as the immobilized oligopeptide or oligonucleotide, anticipating present claim 8.

3. Claims 1, 2, 3, 10, and 13 are rejected under 35 U.S.C. 102(b,e) as being anticipated by Fodor et al. U.S. patent 5,424,186 (June 1995).

The Fodor et al. reference discloses a method for synthesizing oligonucleotides on a solid substrate, or support (abstract). The method of Fodor et al. is performed in a "non-oxidizing atmosphere" in accordance with applicant's definition as evidenced by column 50, lines 23-37 in which Fodor et al. refers to the selection of protecting groups "*they are stable (that is, they remain attached to the molecule) to the synthesis reaction conditions; they are removable under conditions that do not adversely affect the remaining structure etc.*" Applicant states in the specification (as was known in the art at the time of the Fodor et al. invention) that ozone reacts with nucleic acids. Fodor et al. states that conditions for removing protecting groups do not adversely affect the remaining structure, indicating that, at least for the steps that involve removal of the protecting groups, there is no degradation of nucleic acid and the environment is "non-oxidizing" according to applicant's definition. Additionally, in example 3, columns 66-68, a poly dT made according to Fodor et al. was able to hybridize to poly dA probes even after an overnight incubation in 1X SSPE buffer at 40 deg. C. This too indicates that Fodor et al. used conditions that qualify as a "non-oxidizing atmosphere" for synthesis, hybridization, and storage of oligonucleotide arrays, anticipating present claims 1, 2, and 13. Applicant's figure 1A indicates that concentrations of ozone as low as 5 ppb results in 70% degradation of poly T within 15 hours of exposure. It appears that the solutions used by Fodor et al. did not contain levels of ozone (e.g. 5 ppb) sufficient to cause degradation of poly dT, anticipating present claim 3. According to column 67, lines 12-17, the poly dT array was "*dried with N2 and stored in the*

*dark under vacuum*." This anticipates present claim 10, which recites packaging a nucleic acid array "*in an enclosure having a non-oxidizing atmosphere*."

**Claims Rejections – 35 U.S.C. 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, 3, and 7-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terrett, N.K., "Combinatorial Chemistry" (1998) Oxford University Press, pp. 40-47.

Pages 40-47 of the Terrett reference summarize the teachings of a number of methods for light-directed parallel synthesis including the synthesis of peptides and oligonucleotides using the VSLIPS or very large scale immobilized peptide synthesis method. Pages 43-47 of the reference teach that VSLIPS can be used for peptide or oligonucleotide synthesis. Page 43 of the Terrett reference also teaches a "channel" method. Both the "channel" method and the photolithography method involve the activation of a support, attaching nucleotides to the support in defined regions that are not "masked", the use of protecting groups, and cycles of nucleotide additions in which the pattern of the mask changes to allow reactions to occur at specified sites on the solid substrate (see page 43, second paragraph through page 45, first paragraph). The source of UV light used in light-directed parallel synthesis as disclosed on page 41 of Terrett is on the same side of the glass slide as the immobilized oligopeptide or oligonucleotide.

The Terrett reference does not explicitly teach a "non-oxidizing atmosphere" and is silent with respect to ozone concentrations in the solutions used during synthesis, storage, or screening. The Terrett reference does not explicitly teach the use of carbon-filtered air, argon, or inert gasses in combination with VSLIPS technology.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to synthesize and package oligonucleotide arrays under conditions "*that produce less*

*than 30% degradation of nucleic acid over a period of about 1 hour at ambient temperature (about 18 to about 25°C).*" One would have been motivated to do so because the arrays were intended for screening and diagnostic applications for which oligonucleotide integrity is critical. One would have had reasonable expectation for success because the arrays cited in the Terrett reference were successfully used to screen HIV-1 RNAs (pages 45-46). Accordingly, present claims 1, 2, 8, 10, and 13 are unpatentable over the Terrett reference.

Though silent with respect to the concentration of ozone in the "atmosphere," it is apparent that the methods for making oligonucleotide arrays produced arrays that were fully functional in binding assays, indicating that ozone concentrations did not adversely affect the libraries. Therefor the concentrations of ozone in the "non-oxidizing atmosphere" as defined by applicant must have been in the range of "about 0 to about 5 ppb." Consequently, present claims 3, 11, and 14 are unpatentable over Terrett.

The spatial relationship between the solid substrate and light source for photolithographic techniques was a matter of design choice well within the abilities of one of ordinary skill in the art. Consequently, present claims 7 and 9 are unpatentable over Terrett. The amount of time that passes from the making of an array to the packaging of the array is also a matter of design choice. One of ordinary skill in the art would have been motivated to package arrays quickly (e.g. in less than 2 hours) to avoid contamination and decomposition caused by light and/or oxidation. Consequently, present claim 12 is unpatentable over Terrett

5. Claims 1, 2, 3, and 7-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terrett, N.K., "Combinatorial Chemistry" (1998) Oxford University Press, pp. 40-47 and Fodor et al. U.S. patent 5,424,186 (June 1995).

Pages 40-47 of the Terrett reference summarize the teachings of a number of methods for light-directed parallel synthesis including the synthesis of peptides and oligonucleotides using the VSLIPS or very large scale immobilized peptide synthesis method. Pages 43-47 of the reference teach that VSLIPS can be used for peptide or oligonucleotide synthesis. Page 43 of the Terrett reference also teaches a "channel" method. Both the "channel" method and the photolithography method involve the activation of a support, attaching nucleotides to the support in defined regions that are not "masked", the use of protecting groups, and cycles of nucleotide

additions in which the pattern of the mask changes to allow reactions to occur at specified sites on the solid substrate (see page 43, second paragraph through page 45, first paragraph). The source of UV light used in light-directed parallel synthesis as disclosed on page 41 of Terrett is on the same side of the glass slide as the immobilized oligopeptide or oligonucleotide.

The Terrett reference does not explicitly teach a "non-oxidizing atmosphere" and is silent with respect to ozone concentrations in the solutions used during synthesis, storage, or screening. The Terrett reference does not explicitly teach the use of carbon-filtered air, argon, or inert gasses in combination with VSLIPS technology.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to synthesize and package oligonucleotide arrays under conditions "*that produce less than 30% degradation of nucleic acid over a period of about 1 hour at ambient temperature (about 18 to about 25°C).*" One would have been motivated to do so because the arrays were intended for screening and diagnostic applications for which oligonucleotide integrity is critical. One would have had reasonable expectation for success because the arrays cited in the Terrett reference were successfully used to screen HIV-1 RNAs (pages 45-46). Accordingly, present claims 1, 2, 8, 10, and 13 are unpatentable over the Terrett reference.

Though silent with respect to the concentration of ozone in the "atmosphere," it is apparent that the methods for making oligonucleotide arrays produced arrays that were fully functional in binding assays, indicating that ozone concentrations did not adversely affect the libraries. Therefor the concentrations of ozone in the "non-oxidizing atmosphere" as defined by applicant must have been in the range of "about 0 to about 5 ppb." Additionally, the Fodor et al. reference teaches a method for synthesizing oligonucleotides on a solid substrate, or support. In example 3, columns 66-68 of Fodor et al., a poly dT made according to Fodor et al. was hybridized to poly dA probes even after an overnight incubation in 1X SSPE buffer at 40 deg. C. This indicates that Fodor et al. used conditions that qualify as a "non-oxidizing atmosphere" for synthesis, hybridization, and storage of oligonucleotide arrays. Applicant's figure 1A indicates that concentrations of ozone as low as 5 ppb results in 70% degradation of poly T within 15 hours of exposure. It appears that the solutions used by Fodor et al. did not contain levels of ozone (e.g. 5 ppb) sufficient to cause degradation of poly dT. Claim 3 is therefore unpatentable over Terrett and Fodor et al.

According to column 67, lines 12-17, the poly dT array was "*dried with N2 and stored in the dark under vacuum.*" Thus, present claim 10, which recites packaging a nucleic acid array "*in an enclosure having a non-oxidizing atmosphere*" is unpatentable over Fodor et al.

The spatial relationship between the solid substrate and light source for photolithographic techniques was a matter of design choice well within the abilities of one of ordinary skill in the art. The Fodor et al. reference does not require the light source to be specifically on one side of the solid substrate or the other. Consequently, present claims 7 and 9 are unpatentable over Fodor et al. The amount of time that passes from the making of an array to the packaging of the array is also a matter of design choice. One of ordinary skill in the art would have been motivated to package arrays quickly (e.g. in less than 2 hours) to avoid contamination and decomposition caused by light and/or oxidation. Consequently, present claim 12 is unpatentable over Terrett and Fodor et al.

6. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terrett, N.K., "Combinatorial Chemistry" (1998) Oxford University Press, pp. 40-47, Fodor et al. U.S. patent 5,424,186 (June 1995), and Urdea et al. U.S. Patent No. 4,517,338 (May 1985).

Present claim 3 is unpatentable over the Terrett and Fodor et al. references for reasons provided in preceding paragraph 5. The Terrett and Fodor et al. references do not explicitly teach the use of inert gasses such as argon or carbon-filtered air.

The use of inert gas environments during chemical synthesis is well known in the art and has been used, for example, to protect reagents from reacting with water vapor found in ambient air. The following reference illustrates one of the uses of inert gasses during automated nucleic acid synthesis. The Urdea et al reference teaches a method for synthesizing polynucleotides (abstract). Column 8, lines 1-4, for example, teaches the use of a dry inter gas to move reagents into and through a reaction chamber.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to conduct automated nucleic acid synthesis in the presence of an inert gas such as argon, nitrogen, helium, or carbon filtered air to protect the reagents from reacting with water or other reactive components in the atmosphere. One would have had reasonable expectation for success because this was a standard procedure for nucleic acid synthesis at the time.

7. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terrett, N.K., "Combinatorial Chemistry" (1998) Oxford University Press, pp. 40-47, Fodor et al. U.S. patent 5,424,186 (June 1995), and Brennan U.S. Patent No. 5,814,700 (September 1998).

Present claim 3 is unpatentable over the Terrett and Fodor et al. references for reasons provided in preceding paragraph 5. The Terrett and Fodor et al. references do not explicitly teach the use of inert gasses such as argon or carbon-filtered air.

The use of inert gas environments during chemical synthesis is well known in the art and has been used, for example, to protect reagents from reacting with water vapor found in ambient air. The Brennan reference column 8, lines 40-55 teaches that water and oxygen are to be excluded from reaction chambers in which phosphoramidites are used to synthesize nucleic acids because "*Phosphoramidites are sensitive to hydrolysis by tracing of water, and to oxidation by contact with air.*" The reference teaches that inert gas is used to "*sweep air and water traces from the chamber*" to reduce, if not eliminate hydrolysis and oxidation.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to conduct automated nucleic acid synthesis, including the synthesis of nucleic acid arrays, in the presence of an inert gas such as argon, nitrogen, helium, or carbon filtered air to protect the reagents from reacting with water or other reactive components in the atmosphere. One would have had reasonable expectation for success because this was a standard procedure for nucleic acid synthesis at the time.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas Prasthofer** at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

Thomas Prasthofer, Ph.D., September 6, 2001

BENNETT CELSA
PRIMARY EXAMINER